REMARKS

With this response, claims 37-39, 41-53, 61-64 and 73-77 are pending. Claims 1-36, 40, 54-60 and 65-72 were previously canceled without prejudice or disclaimer. Claims 61-64 and 73-76 have been withdrawn from further consideration by the Examiner as being drawn to non-elected inventions.

Claims 37-39, 41-53, 61, 64 and 77 have been amended. Support for these amendments can be found in the specification as filed, at least, for example, at pages 23-25, and in the original claims. No new matter is entered by way of these amendments.

1. Rejections under 35 U.S.C. § 112

Claims 42 and 43

Claims 42 and 43 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Applicants respectfully disagree.

In response to Applicants' previous assertion that a person of ordinary skill in the art would recognize that binding affinities are expressed in terms of a dissociation constant, and that dissociation constants are well-known by those in the art to have molar (M) units, the Examiner states that "whether or not binding affinity is generally defined in molar units; neither the specification nor the claims define or limit the binding affinity to such units." *Office Action dated February 22, 2010*, at page 4. Claims 42 and 43 are amended herein to recite that the binding affinity of the first binding domain for the molecule has molar (M) units.

Applicants respectfully note that the amendments to claims 42 and 43 do not add new matter despite the Examiner's allegation that the specification does not define or limit the binding affinity to molar units. Applicants note that every claim feature need not be described exactly in the specification because there is no *in haec verba* requirement. *See*, *MPEP* § 2163. Rather, all that is required is "reasonable clarity." *See, MPEP* § 2163.02. Further, an amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of the error in the specification, but also recognize the appropriate correction. *MPEP* § 2163 (citing *In re Oda*, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971)). As stated previously, it is reasonably clear to a person of ordinary skill in the art that

binding affinities are expressed in terms of a dissociation constant, and that dissociation constants are well-known by those in the art to have molar (M) units. *See, e.g.*, Alberts, *et al.* (2008). *Molecular Biology of the Cell*. New York, NY: Garland Science, Taylor & Francis Group, LLC. Accordingly, amending the claims to clarify such does not add new matter.

Applicants respectfully submit that claims 42 and 43 are definite, and submit that the Examiner's rejection of these claims under 35 U.S.C. § 112, second paragraph, has been overcome and should be withdrawn.

Claims 37-39, 41-53 and 77

Claims 37-39, 41-51 and 77 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to satisfy the written description requirement and as allegedly not enabling. In particular, it is alleged that "in absence of a description of the structure and function of the MLL proteins encompassed by the claims, the specification has not provided an adequate written description of the claimed compounds for binding to it for its dyslocalization." *See*, *Office Action dated February 22, 2010*, at page 8. The specification, "while being enabling for a purified compound comprising a first domain for a tumor-specific molecule selected from the group consisting of AML1-ETO, BCR-Abl, PML-RARalpha, PLZF-RARalpha, and EWS-FLI fusion protein and a second binding domain, wherein said compound is a peptide, oligoprotein, protein, or fusion protein, to effect dyslocalization of said tumor-specific molecule, wherein said dyslocalization is to a site where said tumor-specific molecule is not normally present in tumor cells," is allegedly not enabled for the tumor-specific molecule MLL. *Id.*, at pp. 9-10. Finally, it is alleged that the term "MLL" is a relative term which renders the claims indefinite. *Id.*

Without acquiescing to the allegation, and solely for the purpose of expediting prosecution, "MLL" has been deleted from claim 37. Accordingly, Applicants respectfully submit that claims 37-39, 41-51, and 77 satisfy the written description, definiteness, and enablement requirements of 35 U.S.C. § 112. As such, Applicants respectfully request withdrawal of the rejections on these bases.

Claims 52 and 53

In the paragraph summarizing the alleged bases for rejecting the claims as not enabled, the Examiner notes that "the specific compounds of claims 52 and 53, which are compounds that effect dyslocalization of AML1-ETO, would not be expected to bind to and delocalize all of the

claimed tumor specific molecules as these molecules do not contain binding domains for all the tumor specific molecules claimed." *Office Action dated February 22, 2010*, at p. 14. Applicants respectfully assert that the specific compounds of 52 and 53 are not required to delocalize all or even more than one of the molecules enumerated in the claims. Solely in order to facilitate prosecution, Applicants have amended claim 37 to recite"wherein said first binding domain binds one molecule selected from the group consisting of AML1-ETO, BCR-Abl, PML-RARalpha, PLZF-RARalpha, and EWS-FLI." In other words, as long as the specific compounds of claims 52 and 53 comprise a first binding domain that binds one of AML1-ETO, BCR-Abl, PML-RARalpha, PLZF-RARalpha, or EWS-FLI, claims 52 and 53 are enabled. Indeed, the Examiner recognizes that claims 52 and 53 are compounds that effect dyslocalization of AML1-ETO. *Id.* As such, Applicants respectfully submit that rejection of these claims as not enabled because they may not bind, e.g, BCR-Abl, PML-RARalpha, etc., is contrary to established case law and claim interpretation. As such, Applicants respectfully assert that claims 52 and 53 are enabled and respectfully request their immediate allowance as such.

2. Claim Objections

Claim 41

Claim 41 is objected to under 37 C.F.R. § 1.75(c) as allegedly being in improper dependent form. In particular, it is alleged that claim 41 is "drawn to a tumor specific molecule that is a peptide, oligopeptide, protein, or fusion protein, which is broader in scope than the tumor specific molecule of claim 37." *Office Action dated February 22, 2010*, at page 8. Without acquiescing to the allegations, and solely for the purpose of expediting prosecution, the language "wherein the tumor-specific molecule is a peptide, oligopeptide, protein, or a fusion protein" has been deleted and replaced with "wherein the molecule affects survival of the tumor cell." Support for the amendment may be found in the specification as filed, *see, e.g.*, *Specification*, at pp. 23-25 (describing the ability of GFP-M&M to affect the survival of 32D tumor cells).

3. Rejections under 35 U.S.C. § 102

Claims 37-39, 41-45 and 47 remain rejected under 35 U.S.C. § 102(b) as allegedly anticipated by McWhirter *et al.* (Mol. And Cell. Biol. 1993, 13:7587-7595, hereinafter "McWhirter") as evidenced by Wu *et al.* (Oncogene 1999 18:4416-24, hereinafter "Wu").

Additionally, claims 37-39, 41-45, 47-49, and 77 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by WO 01/73433A2 (Minucci et al. October 4, 2001; hereinafter "Minucci") as evidenced by Nussey and Whitehead (Endocrinology: An Integrated Box 3.9, 2001, hereinafter "Nussey"). Further, claims 37-39, 41-49, and 77 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Melnick et al. (Blood 2000, 96:3939-47; hereinafter "Melnick"). Finally, claims 37-39, 41-49, 51 and 77 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Mao et al. (Molecular and Cellular Biology 1999, 19:3635-47; hereinafter "Mao"). Applicants respectfully disagree for the following reasons:

McWhirter

It is alleged that BCR, as disclosed by McWhirter, is encompassed by the claims for the dyslocalization of BCR-Abl and that "BCR can interact with BCR-Abl through the coiled coil domain and second binding domains for binding distinct proteins, BCR would be a purified compound comprising a first binding domain, the coiled coil domain, for BCR-Abl and a second binding domain, SH2 or RacGAP, to effect dyslocalization of BCR-Abl." *Office Action dated February 22, 2010*, at page 15. Without acquiescing to the allegations, and solely for the purpose of expediting prosecution, the claims as amended are directed toward fusion proteins. Applicants respectfully assert that McWhirter does not disclose or suggest a fusion protein comprising a first binding domain and a second binding domain, wherein said first binding domain binds one molecule selected from the group consisting of AML1-ETO, BCR-Abl, PML-RARalpha, PLZF-RARalpha, and EWS-FLI and said second binding domain effects dyslocalization of said molecule, wherein said dyslocalization is to a site where said tumor-specific molecule is not normally present in tumor cells.

As McWhirter does not disclose, expressly or even inherently, every element of the present claims either alone or as evidenced by Wu, Applicants respectfully submit that the Examiner's rejection of claims 37, 41-45 and 47 under 35 U.S.C. § 102(b) has been overcome and should be withdrawn.

Minucci

Claims 37-39, 41-45, 47-49, and 77 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Minucci. In particular, it is alleged that Minucci teaches fusion proteins comprising the coiled coil (CC) region of the transcription factor PML with p53, RBCC, GFP, or

human thyroid nuclear receptor (TR). *See, e.g., Office Action dated February 22, 2010*, at pp. 17-21. It is alleged that these fusion proteins comprise a first binding domain for PML-RAR since the fusion proteins comprise the coiled coil domain. *See, id.* It is further alleged that p53, RBCC, or human thyroid nuclear receptor (TR) is a second binding domain to effect dyslocalization. *See, id.* Applicants respectfully disagree that Minucci anticipates claims 37-39, 41-45, 47-49, and 77, even if taken in light of Nussey.

In particular, Applicants note that Minucci does not teach that the fusion proteins disclosed therein, and particularly the coiled coil regions of said fusion proteins, bind to a molecule selected from the group consisting of AML1-ETO, BCR-Abl, PML-RARalpha, PLZF-RARalpha, and EWS-FLI. In fact, Minucci teaches that the fusion of the coiled coil domain of PML to "target protein" (e.g., p53, thyroid nuclear receptor) causes a disruption in the normal oligomerization or binding pattern of the target protein. For example, Minucci does not teach that CC-p53 binds PML-RARalpha, but rather, teaches that CC-p53 binds other CC-p53 proteins and wildtype p53 proteins. *See, Minucci*, at pp. 61-63. In fact, CC-p53 interacting with wildtype p53 blocked its transcriptional activity. *See, id.* Similarly, Minucci does not teach that CC-TR binds PML-RARalpha, but rather, that CC-TR binds NCoR/HDAC even in the absence of a ligand. *See, id.*, at p. 59. Finally, Minucci teaches that, although CC-RBCC associates with PML-RAR, it reduces its oligomerization, not effects its dyslocalization. *See, id.*, at pp. 59-60. In fact, Minucci reportedly chose RBCC to target PML-RARalpha "to the appropriate nuclear compartment." *See, id*, at p. 60.

As discussed above, the CC fusion proteins described in Minucci did not result in binding of ML1-ETO, BCR-Abl, PML-RARalpha, PLZF-RARalpha, and EWS-FLI and/or specific dyslocalization of any one of these molecules to a site where it is not normally present in tumor cells. Therefore, Minucci does not expressly disclose every element of the present claims, Applicants respectfully submit that the Examiner's rejection of claims 37-39, 41-45, 47-49, and 77 has been overcome and should be withdrawn.

Melnick

Claims 37-39, 41-49, and 77 are rejected as allegedly anticipated by Melnick. In particular, it is alleged that AML1/ETO can interact with PLZF through the ETO domain, and given that AML1/ETO disrupts localization of PLZF, "AML1/ETO would be a purified

compound comprising a first binding domain, ETO, for PLZF-RARα and a second binding, AML1, to effect dyslocalization of PLZF-RARα. Similarly, given that PLZF-RARα has a first binding domain for AML1/ETO and a second binding domain, the DNA binding domain for binding the retinoic acid response, PLZF-RARα would be a purified compound comprising a first binding domain, PLZF, for AML1/ETO and a second binding, RARα, to effect dyslocalization of AML1/ETO." *See Office Action dated February 22, 2010*, at p. 20. Applicants respectfully disagree.

Applicants respectfully assert that, while AML1/ETO binding to PLZF may disrupt localization of wildtype PLZF, the Examiner has not shown that it effects dyslocalization of PLZF/RARα, wherein said dyslocalization is to a site where said molecule is not normally present in tumor cells. Indeed, Melnick reports the opposite. "AML1/ETO could bind to PLZF and severely impair its ability to repress transcription, whereas ETO **enhanced** transcriptional repression mediated by PLZF/RARα." *Melnick*, at p. 3939 (emphasis added). Melnick also states "the addition of ETO significantly **enhanced** repression of RARE reporter by PLZF/RARα, but did not enhance repression by RARα or PML/RARα. . . . This may further explain the potent ability of PLZF/RARα to inhibit RARα target genes, block cellular differentiation, and induce a refractory form of leukemia." *Id.*, at pp. 3945-3946 (emphasis added). In other words, and as stark evidence against the Examiner's assertions, AML1/ETO has a different effect on PLZF and PLZF/RARα. Further, the apparent fact that ETO enhances transcriptional repression by PLZF/RARα indicates that it does not dyslocalize PLZF/RARα to a site where PLZF/RARα is not normally present in tumor cells. As such, Melnick does not disclose every element of the present claims. Accordingly, Applicants respectfully submit that the Examiner's rejection of claims 37-39, 41-49, and 77 under 35 U.S.C. § 102(b) has been overcome and should be withdrawn.

Mao

Claims 37-39, 41-49, 51 and 77 are rejected as allegedly anticipated by Mao. In particular, it is alleged that "[g]iven that MEF has a first binding domain, EID, for AML1/ETO and a second binding domain, the DNA binding domain for binding the IL-3 promoter, MEF would be a purified compound comprising a first binding domain, EID, for AML1/ETO and a second binding [sic], the DNA binding domain to effect dyslocalization of AML1/ETO." *Office*

Action dated February 22, 2010, at p. 21. Applicants respectfully assert that MEF, similar to BCR disclosed by McWhirter, is not a fusion protein as recited by the present claims. As such, Mao does not expressly disclose every element of the present claims. Accordingly Applicants respectfully submit that the Examiner's rejection of claims 37-39, 41-49, 51 and 77 under 35 U.S.C. § 102(b) has been overcome and should be withdrawn.

Having distinguished the independent claims from the art of record, the claims dependent therefrom are patentable for at least the same reasons. However, Applicants reserve the right to separately address the patentability of those claims in the future, should that be necessary.

CONCLUSION

In view of the above, each of the presently pending claims is believed to be in condition for immediate allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding objection and rejections of the claims, and to pass this application to issue. The Examiner is encouraged to contact the undersigned at (202) 942-5068 should any additional information be necessary for allowance.

Respectfully submitted,

/David R. Marsh/

David R. Marsh (Reg. No. 41,408)
Kristan L. Lansbery (Reg. No. 53,183)
Rita S. Wu (Reg. No. 58,285)

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ARNOLD & PORTER LLP
Attn: IP Docketing Dept.
555 12th Street, N.W.
Washington, D.C. 20004
(202) 942-5000 telephone
(202) 942-5999 facsimile